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ORIGINAL ARTICLE

Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development

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Abstract Ovarian carcinoma is the deadliest gynecological malignancy. Previous studies have suggested that the fallopian tube may be the primary site for high-grade serous carcinoma. In prophylactic salpingo-oophorectomies from women with hereditary high risk for ovarian cancer, precursors can be assessed prior to onset and studied as a model for serous cancer precursor lesions. Epidemiologic studies indicate that carcinogenesis may be a result of chronic fallopian tube injury. The aims of this study were to (1) to examine the incidence of serous tubal intraepithelial carcinoma (STIC) in relation to other clinical parameters and (2) to evaluate whether chronic fallopian tube injury was related to cancer development. This study enrolled 101 women, comprising the following three groups: hereditary (n = 60), sporadic serous cancer (n = 18; endometrial cancers were excluded), and control (n = 23). The cases were histologically examined and clinical risk factors were collected. The histological changes were compared between different patients and correlated to clinical risk factors. STICs were identified primarily on the fallopian tube fimbria. The incidence of STIC was 3 % in the hereditary patients. In sporadic serous cancer cases, 61 % were associated with STIC and tubal carcinoma ($p < 0.001$). No differences in tubal injury or inflammation were seen when comparing the sporadic serous cancer group and the control group or within the hereditary group. STIC and invasive cancer were seen more often in the older patients than in the younger patients (p = 0.528). This small study, no correlation with chronic tubal injury or inflammation was identified.

Keywords Fallopian tubes · Ovary · Carcinoma in situ · Inflammation · Serous cystadenocarcinoma

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Introduction

Ovarian cancer is the deadliest gynecological malignancy [11]. More than 22,000 women developed ovarian cancer in the USA in 2014, of which approximately 14,000 women died from their disease [28]. These tumors are, in more than 75 % of the patients, discovered at a late stage, and the rate of mortality is therefore high. It is thus important to understand the early lesions of ovarian cancer [2]. A better knowledge of premalignant lesions is a necessary foundation on which to build prevention and screening programs for ovarian cancer.

The pathogenesis of ovarian cancer is diverse, and the origin of high-grade serous carcinoma still remains controversial. High-grade serous carcinomas account for approximately 80 % of all ovarian cancers [11, 24], and it is the histologic type of ovarian cancer that is most commonly diagnosed in women who have mutations in the breast cancer susceptibility gene (BRCA) [26]. Approximately 11.7–15.3 % of women with ovarian cancer have a family history of cancer, of which the majority has an inherited mutation in BRCA1 or BRCA2 [17, 19]. Systematic examination of fallopian tubes and ovaries removed for prophylactic reasons from women with BRCA mutation has suggested that the fallopian tube is the origin of high-grade ovarian serous carcinomas [2, 3, 7, 14,

21, 23, 26]. In these patients, adnexa are removed before cancer develops and progresses, and lesions found in these specimens can therefore be seen as a model for serous cancer precursor lesions [11, 14, 26].

Many studies have shown that early stages of ovarian cancer can be found in the fallopian tube rather than the ovary [2, 6, 7, 14, 26], but it is still not known where precursor lesions develop [23, 26]. Several candidates for high-grade ovarian cancer precursors have been proposed, including serous tubal intraepithelial carcinomas (STICs), p53 signatures, and secretory cell outgrowths (SCOUTs) [9, 10].

More than 70 % of non-hereditary (sporadic) ovarian cancer and high-grade serous carcinoma show tubal involvement, such as STIC, and roughly 5–8 % of the specimens from bilateral salpingo-oophorectomies (BSOs) have an occult cancer. STIC is a precursor that can be assessed histologically, and it is the earliest form of high-grade serous carcinoma with recognizable morphology [11, 15]. About 50 % of high-grade serous carcinomas that are classified as primary ovarian cancer are associated with STIC, thereby suggesting a connection between them.

Several groups have hypothesized that inflammation of the fallopian tube is a cause of ovarian malignancies. Theories that promote this view suggest that ovulation, menstrual cytokines, or infection may act as a stimulus for a precursor to form [23, 29]. Evidence for associations between chronic inflammation and cancer are accumulating. It has been proposed that chronic inflammation leads to rapid cell division and intensifies the risk for DNA replication errors, particularly in loci that codes for tumor suppression. Inflammation also increases the concentrations of toxic oxidants, which may damage the DNA. The fallopian tubes are frequently exposed to inflammatory agents, in processes such as retrograde flow during menstruation or sexually transmitted infections [22]. Gaytán et al. [8] have shown that more macrophages are present in the fallopian tube than in the ovaries, which suggests that the tubes are more prone to chronic inflammation. Risch and Howe [22] have shown that pelvic inflammatory disease (PID) increases the risk of developing ovarian cancer, while Seidman et al. [25] have shown that chronic salpingitis is present in 50 % of serous carcinomas. These results support the theory that infection is a contributor to serous carcinoma development. Tone et al. [29], in contrast, believes that ovulation-associated inflammatory signaling enhances serous carcinogenesis. Each ovulation stimulates an acute localized inflammatory event, during which leukocytes infiltrate the epithelium, inflammatory mediators are produced, and the tissue is further remodeled. Tone et al. [29] have shown that fallopian tube samples, collected from females with BRCA1 mutations and obtained during the post-ovulatory luteal phase, have a profile of global gene expression that resembles closely that of high-grade serous ovarian carcinoma. This similarity is not present in BRCA1 samples obtained during the follicular phase, which suggests that high-grade serous cancer is related to inflammation and the presence of cytokines [29]. The authors discuss that the production of inflammatory cytokines and oxidants increase during ovulation and suggest that this leads to DNA damage and mutations in p53. This may then result in a clonal expansion of secretory cells with p53 mutations to give p53 signatures [29].

The aim of this study were to (1) examine the incidence of STIC in relation to other clinical risk factors (age, heredity, identified BRCA status, and metachronous cancer diagnosis) and to (2) evaluate whether chronic fallopian tube injury was related to cancer development.

Materials and methods

Patient cohort

This retrospective case-control observational study included archived patient material removed by surgery at the Karolinska University Hospital, Sweden. Three different cohorts of women were included. The first consisted of 60 women who underwent risk-reducing removal of ovaries and fallopian tubes between the years 2005 and 2012 ("hereditary"). The second group consisted of women that underwent surgical resection of ovarian cancer without a known hereditary component ("sporadic serous cancer group"). The third group consisted of women that underwent salpingectomy for a benign indication ("control").

The two case groups were women with hereditary ovarian cancer risk (women with identified BRCA mutations and women with family history of cancer but no identified BRCA mutation) and, secondly, women with gynecological sporadic serous cancer. Women with endometrial cancer were excluded. Family history was defined as a close relative with breast cancer age 50 or younger or ovarian cancer at any age. The hereditary case group and the sporadic cancer case group included 60 and 18 women, respectively. Mean age at the time of surgery was 52.1 years for all the women with heredity, 53.5 years for women with family history, 51.5 years for BRCA carriers, and 65.6 years for the women with sporadic serous cancer.

The control group consisted of women who have undergone BSO and had benign diagnoses (i.e., benign cysts.). Twenty-three women were included in the control group, and the mean age at the time of surgery was 61.4 years.

Tissue processing, histologic evaluation, and assembly of clinical risk factors

The gynecological specimens included ovaries and fallopian tubes and were retained as formalin-fixed, paraffin-embedded tissue and sectioned into 4-mm intervals in the pathology

archive. Cases were excluded if the fallopian tube was not obtained.

The different cases were identified in the pathology register, and the diagnostic slides were retrieved from the pathology archive. These hematoxylin and eosin (H&E)-stained slides were reviewed in a light microscope (Olympus BX45, Tokyo, Japan). To prevent confirmation bias, all the cases were randomized before examination. STIC, carcinoma, and inflammation were histologically assessed in the fallopian tube and carcinoma and cortical inclusion cysts (CICs) in the ovary. In the cases where areas of atypia could be identified morphologically, confirmatory immunohistochemistry with p53 and Ki-67 was performed.

The pathology register was used to collect the patients' medical records. Clinical risk factors (age, heredity, identified BRCA status, and metachronous cancer diagnosis) were abstracted from the electronic medical record. These risk factors were then tabulated and correlated to the histological findings.

Statistical analyses

Data of STIC and invasive tubal carcinoma were compared within the hereditary case group, between the BRCA subgroup and the family history subgroup. The same data were also compared between the sporadic serous cancer group and the control group. We also examined the differences in percentage of inflammatory signs between the sporadic serous cancer group and the control group and within the heredity group, between cases with STIC and without STIC. Furthermore, in the heredity case group, we examined the differences in percentage of STIC and invasive tubal carcinoma, possible personal history of breast cancer, and identified BRCA mutation between younger (≤45) and older (>45) women. The statistical associations were made in Microsoft Excel 2010. This study used the unpaired two-sample Student's *t* test for continuous variables and Fisher's exact test for categorical variables. *P* value <0.05 was considered statistically significant.

Ethical permission has been obtained for this study from the Regional Ethical Review Board at the Karolinska Institutet.

Results

Patient characteristics

BSOs from a total of 101 women were included in this study. Table 1 summarizes the following three study groups: total hereditary, sporadic serous cancer, and control. The hereditary case group could further be divided into two subgroups, 42 women that were BRCA1 or BRCA2 positive and 18 women who had a strong family history of ovarian carcinoma but not a documented BRCA mutation. The mean age of the study population was 56.6 years with a range from 31 to 91 years. The age in the hereditary case group was lower than that of women in both the sporadic serous cancer group and the control group ($p < 0.001$ and $p = 0.006$). H&E slides from salpingo-oophorectomies were reviewed in all 101 cases. An average of 11.3 (range 2–38) tubal sections and 8.9 (range 2–30) ovarian sections per case were examined.

Frequency of serous tubal intraepithelial carcinoma

STIC was detected in 8 out of the total 101 cases (8 %), including 2 cases from the hereditary group (2/60 hereditary cases = 3 %) and 6 cases from the sporadic serous cancer group (6/18 sporadic cases = 33 %). Out of the 8 cases with STIC, 4 (50 %) were associated with ovarian carcinoma compared to 10 (11 %) of the 92 cases without STIC ($p = 0.012$). The patient characteristics in all cases with STIC can be seen in Table 2, and pictures of the lesions in cases in the heredity group are displayed in Fig. 1. The two cases with STIC in the hereditary case group were all BRCA mutation carriers (5 %) and located to the fimbria or the distal fallopian tube.

Six out of 18 (33 %) cases with sporadic serous carcinoma were diagnosed with STIC, a significant difference in comparison with the control group ($p = 0.004$). The six cases with STIC were all associated with invasive tubal carcinoma, whereas only 42 % of the cases without STIC were associated with invasive tubal carcinoma ($p = 0.038$). Out of these six cases with STIC, four (67 %) were associated with additional invasive tumor involving the ovary (considered primary ovarian cancer) and two (33 %) were associated with invasive tumor in the peritoneum without significant ovarian involvement (considered primary peritoneal). Four of the STICs

Table 1 Number of cases in each patient group and their age at time of surgery

	Overall	Total hereditary	Sporadic serous cancer	Control
Number	101	60	18	23
Age (year)				
Mean (SD)	56.6 (12.89)	52.1 (11.20)	65.6 (10.62)	61.4 (13.63)
Range	31–91	31–76	36–87	40–91

The total study group consists of three groups, total hereditary, sporadic serous cancer, and control

SD standard deviation

Table 2 Patient Characteristics in Cases with STIC

Case no.	Age (year)	Affected gene	Clinical histology	Location, number of foci
7[a]	48	BRCA1	STIC/Inv ca	Fimbria interna, unifocal
10[a]	63	BRCA2	STIC	Fimbria tip, multifocal
65[b]	65	–	STIC	Fimbria tip, multifocal
68[b]	66	–	STIC	Fimbria tip, multifocal
69[b]	70	–	STIC	Tube, multifocal
72[b]	74	–	STIC	Fimbria, multifocal
73[b]	55	–	STIC	Distal tube, multifocal
75[b]	67	–	STIC	Tube, multifocal

STIC serous tubal intraepithelial carcinoma, *Inv ca* invasive carcinoma

[a] Two of the eight cases which were diagnosed with STIC were in the total hereditary group.

[b] Six of the eight cases which were diagnosed with STIC were in the sporadic serous cancer group.

(67 %) were located to the fimbria or the distal fallopian tube, and two cases (33 %) were located to the middle section of the fallopian tube.

Frequency of invasive carcinoma

Invasive tubal carcinoma was found in 12 (12 %) out of the 101 cases, including 1 case with heredity and 11 cases with sporadic serous cancer. Eight (67 %) out of the 12 cases with invasive tubal carcinoma were associated with ovarian carcinoma, compared to 6 out of 89 (7 %) cases without invasive tubal carcinoma ($p < 0.001$). The single case of invasive tubal carcinoma in the hereditary group was from the group of BRCA+ women and, in comparison with the family history group, there was no significant difference. However, there were more lesions in the fallopian tube in the sporadic serous cancer group (61 %) than in the control group (0 %; $p < 0.001$).

Tubal inflammation

Histological signs of inflammation were assessed in the different study groups. Intraepithelial and intrastromal lymphocytes, number of ciliated cells, plical fusion, and length of fimbria were examined.

The correlations between signs of tubal inflammation in cases with and without STIC in the hereditary group, as well as the correlations between the findings of inflammatory signs in the sporadic serous cancer group and the control group, are presented in Table 3. No significant difference could be seen within the hereditary group. A trend could be seen in the comparison between sporadic serous cancer group and the

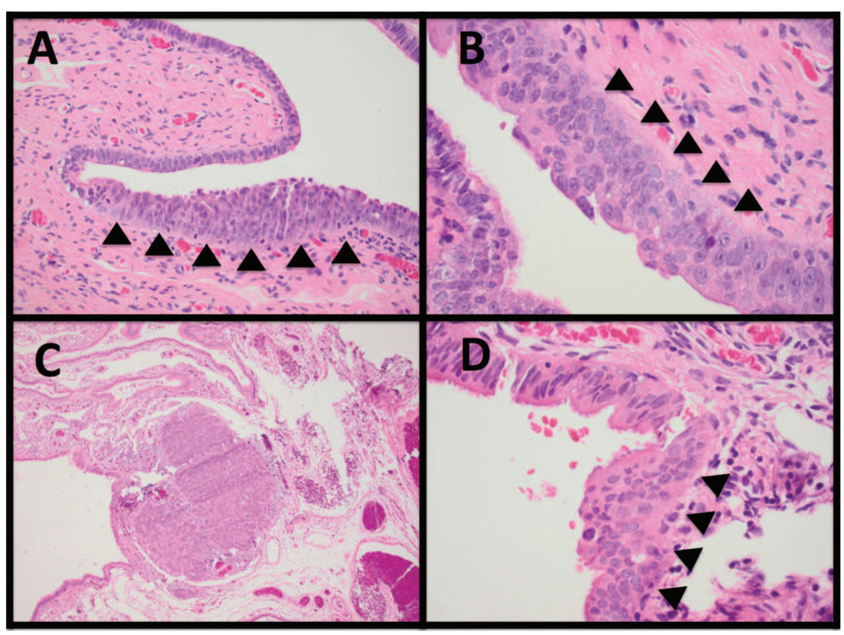

Fig. 1 Two findings of serous tubal intraepithelial carcinoma (STIC) in the hereditary case group. The *black triangles* indicate sections of STIC. **a**, **b** Pictures of STIC found in case no. 10. Multifocal STIC on the fimbria tip, with prominent nucleoli, large nuclei, mitosis, apoptosis, and loss of cell polarity. **c**, **d** Pictures of invasive tubal carcinoma and STIC in case 7. **c** Invasive tumor (1500 μm) associated with STIC (Karin Malmberg/Joseph W. Carlson)

Table 3 Signs of tubal inflammation and comparison between two sets of groups

	Total hereditary					
	With STIC	Without STIC	*P* value	Sporadic serous cancer	Control	*P* value
Number	2	58		18	23	
Ciliated cells[a]	18.8	18.0	0.847	12.1	14.8	0.228
ISL[a]	1.2	1.0	0.835	1.9	1.2	0.140
IEL[a]	2.2	1.8	0.213	3.4	2.3	0.114
Length of fimbria[b]	10.5	9.7	0.696	9.6	8.7	0.408
Plical fusion	0 %	4 %	1.000	0 %	6 %	1.000

A comparison between cases with and without STIC in the hereditary case group and between the sporadic serous cancer group and the control group. Ciliated cells, ISL, IEL, and fimbria length are presented as mean, and the plical fusions are presented as proportion. Ciliated cells, ISL, and IEL are given as number of cells; fimbria length is given in millimeters; and the plical fusion is given as the proportion of its presence. *P* value is calculated with Student's *t* test and Fisher's exact test

STIC serous tubal intraepithelial carcinoma, *ISL* intrastromal lymphocytes, *IEL* intraepithelial lymphocytes

[a] Average of/in 50 epithelial cells in three high-power fields of 40×

[b] Average of the five longest fimbriae

control group; the number of ciliated cells was lower (higher ratio of secretory cells), and the means of intraepithelial and intrastromal lymphocytes were higher in the sporadic serous cancer group.

Discussion

The onset of ovarian serous carcinoma is often insidious [13]; the symptoms are vague and may mimic other conditions. This leads to a late diagnosis. Currently, more than 70 % of women with ovarian cancer are diagnosed when the tumor has spread throughout the abdomen [6, 13], and the 5-year survival rate is approximately 40 % in Sweden today [5]. It has been proposed that a proportion of ovarian carcinomas arise within the fallopian tube, and the present study was aimed to assess pre-malignant lesions of the fallopian tube in women at high risk of developing ovarian carcinoma at the Karolinska University Hospital.

Prevalence of STIC in prophylactic BSO

STIC are usually rare as solitary entities and are more often seen in association with advanced pelvic serous carcinomas [16]. One exception is in patients with a BRCA mutation, where these pre-malignant lesions have been found in prophylactically removed fallopian tubes [16]. Occult cancers have been found in approximately 5–8 % of the specimens from women with a BRCA mutation [4], and Crum et al. [4] showed, in a review of different studies, that 57–100 % of these cancer lesions were found in the fimbriated end of the fallopian tube.

In this study, the prevalence of STIC in risk-reducing salpingo-oophorectomy (RRSO) specimens was 2/60 (3 %). This is at the lower end of studies reported in the literature, but these STIC lesions confirm the earlier publicized location of STIC to the fimbria and the distal fallopian tube.

Prevalence of STIC in women with sporadic serous cancer

The association between BRCA mutation and STIC raises the obvious question whether sporadic serous ovarian cancer, without a history of BRCA mutation, can be linked to the fallopian tube as well. The cancers in these cases are often metastasized throughout the peritoneal cavity, and the location where the cancer has emerged can be hard to define. However, Carlson et al. [1] showed that 47 % of peritoneal serous carcinomas were associated with lesions in the fallopian tube, and Kindelberger et al. [10] demonstrated that approximately 50 % of carcinomas classified as primary serous ovarian tumors were associated with STIC. In this study, 61 % of the cases with a sporadic serous carcinoma were associated with either STIC or invasive tubal carcinoma, a result which is similar to prior studies. This result confirms a connection between sporadic serous carcinoma and STIC, thus indicating that STIC and the fallopian tube are the possible origin of serous ovarian cancer. Of note, the women in the sporadic serous cancer group have no known family history that would indicate a germ line BRCA mutation, but they have not been explicitly tested for a BRCA mutation.

Role of inflammation in the pathogenesis of serous carcinoma

Inflammation has been linked to cancer development in studies. Prior studies have used medical records and questionnaires [20, 22, 27] to collect information concerning previous

relevant PIDs. In this study, we aimed to see if histological signs of inflammation could be associated with ovarian carcinoma and precursor lesions. We examined histologic slides for a lower ratio of ciliated cells, higher number of lymphocytes, longer fimbria length, and plical fusion as marks of inflammation. Previous conclusions concerning the importance of inflammation in ovarian carcinoma development have been inconsistent [12, 18]. Lin et al. [12] as well as Risch and Howe [22] showed a clear association between prior episodes of PID and risk of ovarian cancer, and a study by Seidman et al. [25] indicated that 53 % of ovarian carcinomas are associated with chronic salpingitis. A study made by Shu et al. [27] demonstrated an elevated risk of developing ovarian cancer in patients with a history of PID, although not a statistically significant relationship, whereas Parazzini et al. [20] were able to exclude an increased risk of ovarian cancer in women with previous relevant PID. In our assessment, a trend was confirmed in the comparison between the sporadic serous cancer group and the control group (although not significant). In the cancer group, we noted a slightly lower ratio of ciliated cells, higher number of lymphocytes, and longer fimbria length, indicating increased inflammation. One possible confounder to these results is age. The specimens available for review come from three different surgical procedures, and this impacts the average age of the patient's from which specimens are available. Clearly, age could affect inflammation and could be one possible explanation to some of the results we have found.

This is, to our knowledge, the first time this kind of histological assessment has been performed. The trends identified here provide data for planning future studies. Clinical data, that has been collected from medical record or interviews, may not be entirely accurate; PID is often subclinical (it is not certain that the patient was aware of an infection). In that context, a histological inspection may be more reliable to find a correlation between inflammation and cancer and gives support to this kind of assessment. More research is necessary, aiming to evaluate the possibility that inflammation can damage the tube to a state where mutations occur.

In summary, STIC was found in 2/60 (3 %) of the RRSO specimens and these STIC lesions were localized to the fimbria and the distal fallopian tube, as previously published. In this study population, no significant correlation was made between serous carcinoma and histological signs of inflammation or chronic tubal injury. Additional studies are needed to further evaluate the role of inflammation in carcinogenesis in the fallopian tube and its clinical implications of preventing serous carcinoma.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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Human and animal rights Ethical permission has been obtained for this study from the Regional Ethical Review Board at the Karolinska Institutet.

Informed consent Participants have given their informed consent.

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